

OBSERVATIONS

**Metformin and the Incidence of Cancer in Patients With Diabetes: A Nested Case-Control Study**

**D**iabetes is associated with an increased risk of various forms of cancer, such as cancer of the liver, colon, pancreas, breast, bladder, and kidney. Metformin, widely given to patients with type 2 diabetes, works by inhibiting hepatic glucose production through an LKB1 (serine-threonine liver kinase B1)/AMP-activated protein kinase (AMPK)-mediated mechanism. LKB1 is a well-recognized tumor suppressor. Activation of AMPK by LKB1 plays an important role in inhibiting cell growth. It has been suggested that metformin use in patients with diabetes may reduce their risk of cancer (1). Some studies have reported that diabetic patients taking metformin showed decreased cancer risk (2,3). However, several studies have shown that metformin does not reduce the risk of cancer in patients with diabetes (4,5). Little information is available on the subject considering non-Caucasian ethnicity. We used representative National Health Insurance datasets for Taiwan to form a cohort to assess the total number of cancer incidences in relation to metformin use among diabetic patients.

This study used a sub-dataset composed of 1 million randomly selected

patients from all enrollees registered. We used the ICD-9, Clinical Modification (ICD-9-CM), to identify newly diagnosed diabetic patients and patients who had undergone treatment during the period 1998–2009 (ICD-9-CM 250;  $n = 37,055$ ). We then excluded patients with a history of cancer (ICD-9-CM 140–208) before the diabetes index date. The patients who were diagnosed with malignant cancer (ICD-9-CM 140–208) during the test period were identified as the cancer case group ( $n = 2,158$ ). The patients without a cancer diagnosis before 31 December 2010, matched by age, sex, and study period, were designated as the noncancer group ( $n = 8,609$ ). We then analyzed the effects of metformin use on cancer risk by using a multivariable logistic regression model. All analyses were performed using SAS statistical software (version 9.1 for Windows).

The results showed that there was no significant relationship between metformin use and cancer incidence (odds ratio [OR] 1.06 [95% CI 0.89–1.26]) (Table 1). We also investigated the association between metformin dosage and cancer risk. We used the yearly median dose of metformin as a cutoff point to classify  $<296$  g as low dose and  $>296$  g as high dose of metformin. Using the low-dose group as reference, we did not observe any effect on overall cancer risk whether from use in low dosage (OR 1.03 [95% CI 0.91–1.16]) or in high dosage (OR 0.99 [95% CI 0.87–1.13]).

The results of this cohort study demonstrate that the use of metformin is not associated with a decreased cancer risk, including prostate cancer, several gastroenterological types of cancer, lung

cancer, kidney cancer, and breast cancer, in patients with type 2 diabetes. These results remained unchanged in secondary analyses, in which we adjusted for dose-response, age, sex, and occupation. Additional large population-based unbiased studies are required and would be essential to confirm our current findings before drawing any firm conclusions.

SHU-YI WANG, MD<sup>1</sup>  
 CHIEH-SEN CHUANG, MD<sup>2,3</sup>  
 CHIH-HSIN MUO, MSc<sup>4</sup>  
 SHIH-TE TU, MD<sup>1</sup>  
 MING-CHIA LIN, MSc<sup>5</sup>  
 FUNG-CHANG SUNG, PhD<sup>4,6</sup>  
 CHIA-HUNG KAO, MD<sup>7,8</sup>

From the <sup>1</sup>Departments of Endocrinology and Metabolism, Changhua Christian Hospital, Changhua, Taiwan; the <sup>2</sup>Department of Neurology, Changhua Christian Hospital, Changhua, Taiwan; the <sup>3</sup>Department of Life Sciences, National Chung-Hsing University, Taichung, Taiwan; the <sup>4</sup>Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan; the <sup>5</sup>Department of Nuclear Medicine, E-DA Hospital, I-Shou University, Kaohsiung, Taiwan; the <sup>6</sup>Departments of Public Health, China Medical University, Taichung, Taiwan; the <sup>7</sup>Graduate Institute of Clinical Medicine Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan; and the <sup>8</sup>Department of Nuclear Medicine and Positron Emission Tomography (PET) Center, China Medical University Hospital, Taichung, Taiwan.

Corresponding author: Chia-Hung Kao, d10040@mail.cmuh.org.tw.

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**Table 1—Adjusted OR and 95% CI of cancer for metformin use**

Cancer type (ICD-9-CM)	OR	(95% CI)
Overall (140–208)	1.06	(0.89–1.26)
Prostate cancer (185)	0.94	(0.61–1.46)
Colorectal cancer (153, 154)	0.94	(0.73–1.21)
TCC (188, 189.1–189.9)	0.77	(0.48–1.24)
Liver cancer (155)	0.89	(0.71–1.12)
Lung cancer (162)	1.11	(0.94–1.47)
Stomach cancer (151)	1.62	(0.99–2.64)
Kidney cancer (189.0)	1.74	(0.20–14.9)
Female breast cancer (174)	1.05	(0.70–1.55)
Pancreatic cancer (157)	1.14	(0.68–1.91)
HNCs (140–149)	1.19	(0.76–1.89)
Other	1.03	(0.79–1.34)

Adjusted for age, sex, and occupation. HNCs, head and neck cancers; TCC, transitional cell carcinoma.

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integrity of the data and the accuracy of the data analysis.

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